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*A1 con's*  
*Sub 31*  
(c) identifying one or more polypeptides in said annotated polypeptide index having said characteristics.

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*Sub 32*  
13. (Amended) A method for identifying a polypeptide, comprising:

(a) determining two or more characteristics associated with said polypeptide, or a peptide fragment thereof, one of said characteristics being mass of a peptide fragment of said polypeptide determined by mass spectrometry;

*A2*  
(b) comparing said characteristics associated with said polypeptide to an annotated polypeptide index;

(c) identifying one or more polypeptides in said annotated polypeptide index having said characteristics; and

(d) quantitating the amount of said identified polypeptide in a sample containing said polypeptide.

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REMARKS

Claims 1-43 are currently pending. Claims 1-23 are under examination. Claims 1 and 13 have been amended. The amendment to claims 1 and 13 are supported throughout the specification and the claims as filed. In particular, the amendment to claims 1 and 13 is supported, for example, on page 5, line 25, to page 6, line 4; page 24, lines 25-28; and page 25,

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lines 6-9. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth the amendment to the claims in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining.

Applicants wish to bring to the Examiner's attention co-pending application serial No. 09/748,783.

Regarding the Restriction Requirement

In a telephone conference on November 1, 2001, Examiner Tran indicated that the claims were restricted into two groups as follows:

- Group I: claims 1-23, directed to a method for identifying a polypeptide;
- Group II: claims 24-43, directed to a method for generating a polypeptide identification index.

In a telephone conference on November 8, 2001, the restriction requirement was traversed, and a provisional election of Group I was made. Although the restriction requirement is traversed for the reasons set forth below, Applicants confirm the election of Group I, claims 1-23, for examination.

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The Restriction Requirement is traversed with respect to the division of the claims of Group I from the claims of Group II. While the claims of Groups I and II are patentably distinct, it is submitted that a thorough search of the claims of either group will likely reveal art relevant to the examination of the claims of the other group. This is further indicated by the classification of the claims of Groups I and II in the same class (class 436). Thus, a search of the claims of Group I, which are directed to methods using a polypeptide identification index that is an annotated polypeptide index, will necessarily reveal information relevant to the examination of the claims of Group II, which are directed to methods for generating a polypeptide identification index. Accordingly, division of the claims into these groups would result in duplicative searches. Therefore, examination of the claims of Group II with the claims of Group I together should not be an undue burden on the Examiner, and Applicants respectfully request that Groups I and II be examined together.

Regarding the Information Disclosure Statement

The Office Action indicates that the Information Disclosure Statement faxed on November 30, 2001, fails to comply with the requirements of 37 C.F.R. § 1.98(a)(2). In a conversation with Applicants' representative on November 30, 2001, Examiner Tran indicated that she had not received the Information Disclosure Statement filed on November 2, 2001. Applicants forwarded a copy of the Form 1449 at the Examiner's request. Examiner Tran confirmed on June 12, 2002, that the

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Information Disclosure Statement had still not been received. As requested by Examiner Tran, Applicants attach herewith a copy of the Information Disclosure Statement filed on November 2, 2001, a copy of the postcard showing that the Information Disclosure Statement was received in the U.S. Patent and Trademark Office on January 15, 2002, along with copies of the cited references. Applicants request that these references be considered in the examination of this application and that their consideration be made of written record in the application file.

Applicants also submit herewith an Information Disclosure Statement containing references cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement. Applicants request that these references also be considered in the examination of this application and that their consideration be made of written record in the application file.

Rejection Under 35 U.S.C. § 112

The rejection of claims 1-23 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. The Office Action alleges that claims 1 and 13 are unclear for the use of the term "fragment of the polypeptide." Claims 1 and 13, as amended, are directed to "peptide fragment," and Applicants believe that this term is clear and definite. Accordingly, Applicants respectfully request that this rejection be withdrawn.

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The Office Action also indicates that claims 1 and 13 are indefinite for the term "fragment mass." Claims 1 and 13 have been amended to delete the term "fragment mass." Accordingly, this rejection has been rendered moot and Applicants respectfully request that this rejection be withdrawn.

The Office Action additionally indicates that claims 1 and 13 are unclear for use of the term "annotated polypeptide index." Applicants respectfully submit that the term "annotated polypeptide index" is clear in view of the teachings in the specification. In particular, the specification teaches that an annotated polypeptide index refers to a collection of characteristics associated with a polypeptide sufficient to identify and distinguish other polypeptides in the index and comprising at least one empirically determined characteristic for each of the polypeptides in an index (page 18, line 15, to page 19, line 9). The annotated polypeptide index can be based on empirically determined characteristics or a combination of deduced and empirically determined characteristics. The specification further teaches methods of determining characteristics associated with a polypeptide and generating an annotated polypeptide index (see, for example, page 20, line 30, to page 21, line 13; page 26, lines 12-30; page 30, line 11, to page 32, line 9; page 33, line 3, to page 35, line 2; page 35, line 11, to page 36, line 13; page 37, line 1, to page 41, line 17; page 42, line 19, to page 44, line 3; and Examples I and II on pages 66-78). Therefore, Applicants respectfully submit that the meaning of the term "annotated polypeptide index" is clear

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and definite and respectfully request that this rejection be withdrawn.

The Office Action further indicates that the term "optionally" recited in claim 2, step (f), and claim 14, step (g), is unclear as to whether the step is included in the method. With regard to claim 2, the claim recites steps (d), (e) and (f), where step (f) recites "optionally repeating steps (d) and (e) one or more times, wherein a set of characteristics is determined that identifies a single polypeptide in said annotated polypeptide index." Similarly, claim 14 recites steps (e), (f) and (g), where step (g) recites "optionally repeating steps (e) and (f) one or more times, wherein a set of characteristics is determined that identifies a single polypeptide in said annotated polypeptide index." The claims clearly recite that the previous steps, (d) and (e) in claim 2 and (e) and (f) in claim 14, are optionally repeated one or more times. Accordingly, claim 2 recites steps (d) and (e), wherein a set of characteristics is determined that identifies a single polypeptide in said annotated polypeptide index, and optionally that steps (d) and (e) can be repeated one or more times, wherein a set of characteristics is determined that identifies a single polypeptide in said annotated polypeptide index. Similarly, claim 14 recites steps (e) and (f), wherein a set of characteristics is determined that identifies a single polypeptide in said annotated polypeptide index, and optionally that steps (e) and (f) can be repeated one or more times, wherein a set of characteristics is determined that identifies a single polypeptide in said annotated polypeptide index. Therefore, Applicants believe that the

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meaning of the optional repeating of steps is clear and definite and respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

The rejection of claims 1, 2 and 8-12 under 35 U.S.C. § 102(b) as allegedly anticipated by Yates, J. Mass. Spectrom. 33:1-19 (1998), or Link et al., Nat. Biotechnol. 17:676-682 (1999), is respectfully traversed. Applicants submit that the claimed methods are novel over Yates or Link et al.

Applicants respectfully submit that neither Yates nor Link et al. teach the claimed methods for identifying a polypeptide. In particular, neither Yates nor Link et al. teach a method for identifying a polypeptide by determining two or more characteristics associated with the polypeptide, or a peptide fragment thereof, one of the characteristics being mass of a peptide fragment of the polypeptide determined by mass spectrometry; comparing the characteristics associated with the polypeptide to an annotated polypeptide index; and identifying one or more polypeptides in the annotated polypeptide index having the characteristics, as in claim 1. As taught in the specification, an annotated polypeptide index refers to a polypeptide index in which the collection of characteristics associated with a polypeptide in the index includes at least one empirically determined characteristic (page 18, line 15, to page 19, line 5). In contrast, Yates describes the use of predicted values from database sequences, but not a database using empirically determined characteristics (see page 7, column 2,

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last paragraph, line 10; page 8, Figure 3 legend; page 9, column 2, line 28). Similarly, Link et al. describes the use of standard *Saccharomyces cerevisiae* open reading frames from the *Saccharomyces* genome database, but not a database using empirically determined characteristics (see page 681, lines 8-9 and reference 30, the *Saccharomyces* genome database website). Accordingly, neither Yates nor Link et al. teach the claimed methods using an annotated polypeptide index. Absent such a teaching, Applicants respectfully submit that the claims are novel over Yates or Link et al. and respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

The rejection of claims 3, 13, 14, and 20-23 under 35 U.S.C. § 103 as allegedly obvious over Yates, J. Mass. Spectrom. 33:1-19 (1998), or Link et al., Nat. Biotechnol. 17:676-682 (1999), in view of Mann, Nat. Biotechnol. 17:954-955 (1999), or Gygi et al., Nat. Biotechnol. 17:994-999 (1999), is respectfully traversed. Applicants respectfully submit that the claimed methods are unobvious over Yates or Link et al., alone or in combination with Mann or Gygi et al.

As discussed above, the claimed methods recite the use of an annotated polypeptide index, which refers to a polypeptide index in which the collection of characteristics associated with a polypeptide in the index includes at least one empirically determined characteristic (page 18, line 15, to page 19, line 5). In contrast, Yates describes the use of predicted values from



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database sequences and Link et al. describes the use of standard *Saccharomyces cerevisiae* open reading frames from the *Saccharomyces* genome database, but neither teaches or suggests the use of a database containing empirically determined characteristics. Furthermore, neither Mann or Gygi et al. cure the deficiencies of Yates or Link et al. In particular, neither Mann or Gygi et al., alone or in combination with Yates or Link et al., teach or suggest the claimed method using an annotated polypeptide index. Absent such a teaching or suggestion, Applicants respectfully submit that the claimed methods are unobvious over the cited references. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The rejection of claims 4-8 and 15-19 under 35 U.S.C. § 103 as allegedly obvious over Yates, J. Mass. Spectrom. 33:1-19 (1998), or Link et al., Nat. Biotechnol. 17:676-682 (1999), in view of Masselon et al., Anal. Chem. 72:1918-1924 (2000), is respectfully traversed. Applicants respectfully submit that the claimed methods are unobvious over Yates or Link et al., alone or in combination with Mann or Gygi et al.

As discussed above, the claimed methods recite the use of an annotated polypeptide index, which refers to a polypeptide index in which the collection of characteristics associated with a polypeptide in the index includes at least one empirically determined characteristic (Masselon et al., page 18, line 15, to page 19, line 5). In contrast, Yates describes the use of predicted values from database sequences and Link et al. describes the use of standard *Saccharomyces cerevisiae* open

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reading frames from the *Saccharomyces* genome database, but neither teaches or suggests the use of a database containing empirically determined characteristics. Furthermore, Masselon et al. does not cure the deficiencies of Yates or Link et al. In particular, Masselon et al., alone or in combination with Yates or Link et al., does not teach or suggest the claimed method using an annotated polypeptide index.

The Office Action alleges that it would have been obvious at the time the invention was made to include the method of increasing the accuracy of the mass measured, as disclosed by Masselon et al., with the methods of Yates and Link et al. for identifying a polypeptide in order to maintain the high confidence levels for polypeptide identification by the use of high-accuracy mass measurements (Masselon et al., page 19, left column, lines 12-13). However, in contrast to the description in Masselon et al., the specification teaches that the methods of the invention are advantageous because the combination of additional characteristics allows the determination of mass at lower accuracy, that is higher ppm (page 24, lines 3-24). Applicants point out that the mass accuracy recited in claims 4-8 and 15-19, with increasing ppm values, are respectively directed to decreasing mass accuracy. Therefore, Applicants respectfully disagrees with the assertion in the Office Action that Masselon et al, in combination with Yates or Link et al., renders the claimed methods obvious.

Applicants respectfully submit that the claimed methods are unobvious over Yates or Link et al., alone or in combination

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with Masselon et al. Accordingly, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Date

  
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APPENDIX A

1. (Amended) A method for identifying a polypeptide, comprising:

(a) determining two or more characteristics associated with said polypeptide, or a peptide fragment thereof, one of said characteristics being mass of a peptide fragment of said polypeptide[, said fragment mass being] determined by mass spectrometry;

(b) comparing said characteristics associated with said polypeptide to an annotated polypeptide index; and

(c) identifying one or more polypeptides in said annotated polypeptide index having said characteristics.

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13. (Amended) A method for identifying a polypeptide, comprising:

(a) determining two or more characteristics associated with said polypeptide, or a peptide fragment thereof, one of said characteristics being mass of a peptide fragment of said polypeptide[, said fragment mass being] determined by mass spectrometry;

(b) comparing said characteristics associated with said polypeptide to an annotated polypeptide index;

(c) identifying one or more polypeptides in said annotated polypeptide index having said characteristics; and

(d) quantitating the amount of said identified polypeptide in a sample containing said polypeptide.